PCT/EP 98/01293

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Patentanmeldung Nr. — Patent application No. — Demande de brevet n°

97200646.4

PRIORITY DOCUMENT

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Im Auftrag

For the President of the European Patent Office

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Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

Anmeldung Nr.:
Application no.:
Demande n°: 97200646.4

Anmeldetag:
Date of filing:
Date de dépôt: 05/03/97

Anmelder:
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Bezeichnung der Erfindung:
Title of the invention:
Titre de l'invention:
7alpha-methyl-17alpha-ethynyl-estrane derivative for the treatment of atherosclerosis

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

Staat: State: Pays:	Tag: Date: Date:	Aktenzeichen: File no. Numéro de dépôt:

Internationale Patentklassifikation:
International Patent classification:
Classification internationale des brevets:
A61K31/565

Am Anmeldetag benannte Vertragstaaten:
Contracting states designated at date of filing: AT/BE/CH/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE
Etats contractants désignés lors du dépôt:

Bemerkungen:
Remarks:
Remarques:
The title of the application as originally filed reads as follows:
Use of a 7alpha-methyl-17alpha-ethynyl-estrane derivative for the treatment of atherosclerosis

USE OF A 7α-METHYL-17α-ETHYNYL-ESTRANE DERIVATIVE FOR THE TREATMENT OF ATHEROSCLEROSIS

The present invention relates to the use of a 7α-methyl-17α-ethynyl-estrane derivative for the manufacture of a medicament for the prophylaxis and the treatment of atherosclerosis.

Coronory heart disease (CHD) is a consequence of atherosclerotic processes in the artery vessel wall. The development of atherosclerosis starts with the accumulation of cholesterol in lipoproteins in the vessel wall and the subsequent development of fatty streaks (probably the earliest macroscopically recognizable lesions), which appear in the intima of the arterial vessel wall as focal collections of lipid-filled macrophages ("foam cells"). This process can progress in the formation of advanced lesions; foam cell necrosis and endothelial damage can occur leading to smooth muscle cell migration and proliferation, and to the formation of extracellular matrix. Thus atherosclerosis is the result of the interaction of a number of cell types in the vessel wall, in which increased plasma cholesterol can be the driving force (Davies, M.J., and Woolf, N.; "Atherosclerosis: what is it and why does it occur"; Brit. Heart J., 1993, 69 (suppl.), S3-S11).

It is well known that the incidence of CHD in women in the reproductive stage of life is much lower than in men of similar age but that the risks sharply increase following the menopause. The menopause has been associated with a large number of vasomotor, psychological and gynaecological symptoms, part of which are characteristic for the perimenopausal period (climacteric). The menopause has been shown to be a risk factor for chronic diseases like osteoporosis and atherosclerosis.

The sharply decreasing concentrations of estrogens, especially of estradiol (estra-1,3,5 (10)-triene-3,17-diol) and estron (3-hydroxy-estra-1,3,5

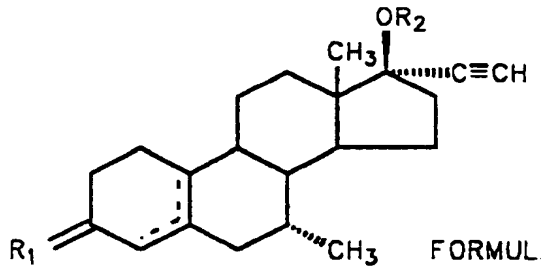
(10)-triene-17-one), in postmenopausal women have been suggested to be related to these symptoms. Estrogen replacement therapy, through which the physiologic deficit of mainly estrogen is to be corrected, is gaining increasing acceptance as a means of alleviating climacteric symptoms in postmenopausal women and preventing osteoporosis. In addition, exogenous estrogen is reported to have a plasma cholesterol- and a LDL (low density lipoproteins)-cholesterol lowering effect and/or a plasma HDL (high density lipoproteins)-cholesterol increasing effect. These estrogen effects may be suggestive of a protective overall effect on the formation of atherosclerotic lesions.

Clinically unopposed estrogen replacement therapy in post menopausal women can increase the risk of endometrial hyperplasia and endometrial cancer. Therefore most therapies under study to date concern combined treatments with both an estrogen component and a progestagen component, which is added to negate the estrogen mediated risks (hormone replacement therapy). Progestagens can have adverse effects on the lipid compositions and antagonize the beneficial effects of estrogen on the arterial vessel.

A synthetic steroid, 7α-methyl-17α-ethynyl-17β-hydroxy-estra-5(10)-en-3-one (Org OD-14; tibolone), produced by Organon, The Netherlands, characterized by having weak estrogenic, progestogenic and androgenic properties, has been shown to be clinically as effective as estradiol valerate or conjugated equine estrogens in reducing climacteric symptoms in perimenopausal women. Tibolone has further been shown, like the long term administration of estrogen, to provide substantial protection against the development of osteoporosis in post menopausal women (Hannover, N. et al., J. Clin. Endocrinology and Metabolism (1996), 81, 2419-2422). The effect of long term treatment with tibolone on HDL-cholesterol has been interpreted as less favorable with respect to its protective effect against cardiovascular disease, as compared with estrogen replacement therapy (Riggs, B.L., J. Clin. Endocrinology and Metabolism (1996), 81, 2417-2418).

Surprisingly, it has now been found that 7α-methyl-17α-ethynyl-17β-hydroxy-estra-5(10)-en-3-one, prodrug forms thereof and certain metabolites thereof have anti-atherosclerotic properties.

The present invention therefore relates to 7α-methyl-17α-ethynyl-estrane derivatives having the general formula I



FORMULA I

wherein

R_1 = H(OR_3) or O; R_2 = H or (C_{1-18})Acyl; R_3 = H or (C_{1-18})Acyl;

and the dotted line represents a double bond in the 4,5- or the 5,10-position, for the manufacture of a medicament for the prophylaxis or the treatment of atherosclerosis.

These compounds, more specifically the compounds wherein R1 is H,OH or O and the double bond is at the 5,10-position, and especially the compound (tibolone; Org OD-14) wherein R1 is O, R2 is H and wherein the double bond is in the 5,10-position, have a very pronounced atheroprotective effect. Contrary to expectation, in view of the weak estrogenic activity of the compounds of the invention, their atheroprotective effect is much stronger in comparison with the atheroprotective effect of 17β-estradiol. The compounds of the invention can therefore be used in mammals as a medicament to protect the arterial vessel wall against atherosclerotic processes.

The term acyl means an acyl group derived from an organic carboxylic acid having 1-18 carbon atoms, as is also indicated by the affix (C_{1-18}).

Examples of such carboxylic acids are formic acid, acetic acid, propionic acid, butyric acid isobutyric acid, trimethylacetic acid, valeric acid, caproic acid, capric acid, undecylenic acid, lauric acid, palmitic acid, oleic acid, phenylacetic acid, phenylpropionic acid, benzoic acid, fumaric acid, maleic acid, succinic acid and citric acid. Preferred acyl groups have 1-6 carbon atoms, and most preferred is the acetyl group.

The 7α-methyl-17α-ethynyl-estrane derivatives according to formula I are known compounds. The compounds can thus be prepared as described, for example, in US Patent 3,340,279 and in US Patent 4,701,450 for 7α-methyl-17α-ethynyl-17β-hydroxy-estra-5(10)-en-3-one (tibolone).

The 7α-methyl-17α-ethynyl-estrane derivatives according to the invention, and pharmaceutical preparations based thereon, have a beneficial effect on the cholesterol accumulation in the vessel wall, the fatty streak formation and the advanced lesion formation. Due to their strong favourable influence on the vascular lesion formation, the 7α-methyl-17α-ethynyl-estrane derivatives according to the invention are suitable for therapeutic use in the treatment of atherosclerosis. Additionally, the 7α-methyl-17α-ethynyl-estrane derivatives can also be used prophylactically. The present invention therefore provides a method of inhibiting the process of atherosclerosis comprising administering to a mammal, preferably to a human, an atheroprotective amount of a 7α-methyl-17α-ethynyl-estrane derivative having the general formula I, as previously defined.

Suitable 7α-methyl-17α-ethynyl-estrane derivatives having general formula I which can be used according to the invention are, for example, 7α-methyl-17α-ethynyl-17β-hydroxy-estra-5(10)-en-3-one (CD-14;tibolone), 7α-methyl-17α-ethynyl-estra-5(10)-en-3α,17β-diol, 7α-methyl-17α-ethynyl-estra-5(10)-en-3β,17β-diol, 7α-methyl-17α-ethynyl-17β-hydroxy-estra-4-en-3-one,

and esters thereof. A particular preferred 7α-methyl-17α-ethynyl-estrane derivative is tibolone (Org OD-14).

The 7α-methyl-17α-ethynyl-estrane derivatives according to the invention may be administered enterally or parenterally and for humans in a daily dosage of 0.05 - 10 mg, preferably 0.1-2.5 mg.

A daily dose can be administered in one or more dosage units through for example the oral, the rectal, the sublingual route, the nasal route or through the skin (for example, transdermal patches, or in the form of a cream). Preferably a single dosage unit a day is administered by the oral route. Alternatively, a controlled release preparation, releasing the daily required total dose as defined above, can be used. Controlled release preparations can be taken by the oral route, or are preferably applied in the form of a subcutaneous implant.

The pharmaceutical preparations for use according to the invention can be prepared in accordance with standard techniques such as for example are described in the standard reference, Gennaro et al. (Ed.), Remmington's Pharmaceutical Sciences, (18th ed. Mack Publishing Company, 1990, e.g. Part 8: Parmaceutical Preparations And Their Manufacture). For the purpose of making the pharmaceutical preparations according to the invention, the 7α-methyl-17α-ethynyl-estrane derivatives according to formula I, or pharmaceutically acceptable salts thereof, are mixed with or dissolved in a pharmaceutical acceptable carrier. Examples of such preparations are tablets, pills, suppositories, (micro-)capsules, powders, emulsions, creams, ointments, suspensions, solutions, implants, or sprays.

Examples of pharmaceutically acceptable carriers are: starch (for example potato or corn starch), sugars (for example lactose), lubricants (for example magnesium stearate), binders (for example amylopectine or polyvinyl pyrrolidone), water, alcohol, glycerol and its derivatives, vegetable-,

animal- and mineral oils and fats, fatty alcohols, silicones, polyalkylene glycols, cellulose derivatives, silica, dispersants, emulsifiers, surfactants, anti-oxidants, colorants and preservatives. In fact, any conventional pharmaceutical carrier that does not interfere with performance of the active ingredient can be used in the preparations according to the present invention.

Pharmaceutical preparations of the preferred 7α-methyl-17α-ethynyl-estrane derivative of the invention, i.e. 7α-methyl-17α-ethynyl-17β-hydroxy-estra-5(10)-en-3-one (Org OD-14; tibolone), are preferably prepared using the crystalline pure monoclinic ($P2_1$) form of Org OD-14, because of its improved stability, bioavailability and shelf-life. The synthesis and use in a pharmaceutical preparation of this monoclinic derivative of Org OD-14 is disclosed in European Patent No. 0,389,035B1.

The atheroprotective properties of 7α-methyl-17α-ethynyl-estrane derivatives according to formula I are revealed in a cholesterol fed rabbit model wherein the effects of the compounds on the atherogenesis in female ovariectomized rabbits are established. The model is considered relevant to the human atherosclerotic process, because the cellular events occurring during the development of the atherosclerotic lesions during the atherogenic diet are similar with those observed in different stages of atherosclerotic processes in coronory arteries.

The invention is illustrated by the following examples:

Example 1

Tablets were prepared from a basic granulate containing lactose (100 mg per tablet) and dried potato starch (10 mg per tablet). The base granules were prepared by mixing the lactose with a portion of the starch. The remainder of the starch was mixed to a slurry with water and added to the mixture. The whole was granulated and dried. These base granules were mixed with ascorbyl palmitate (0.2 mg per tablet) and with either one of OD14 (2 mg or 6 mg per tablet) or 17β-estradiol (4 mg per tablet), sieved, finely mixed with magnesium stearate (0.5 mg per tablet) and then tabletted.

Example 2.

An experiment was performed with 7 groups of sexually mature, virgin female New Zealand White rabbits (Harlan, Zeist, The Netherlands), age 7-9 months and weighing approximately 3 kg (number of rats per group: 13-14). During the acclimatization period the rabbits were fed a diet of standard commercial rabbit chow LKK20 (Hope Farms, Woerden, The Netherlands). Three weeks prior to the start of the experiment the animals were anaesthetized and underwent bilateral ovariectomy (OVX) or were sham operated. After three weeks, at the start of the experiment, the rabbits were randomized over the treatment groups. In all animals de-endothelialisation of a segment of the left carotid artery was applied by using the air-drying technique (Fishman, J.A. et al., "Endothelial regeneration in the rat carotid artery and the significance of endothelial denudation in the pathogenesis of myointimal thickening", Lab. Invest. 1975, 32, 339-351; and Lafont, A. et al., "Restenosis and experimental angioplasty: Intimal, medial and adventitial changes associated with constructive remodeling", Circulation Research, 1995, 76, 996-1002)

The animals were randomly allocated into 7 experimental groups using a randomized block design. The groups wer fed an atherogenic diet

(commercial rabbit chow (LKK20) enriched with 0.4 grams cholesterol, 3.75 grams coconut oil and 3.75 grams peanut oil per 100 grams). One group was fed the standard rabbit chow (LKK20). Food intake was restricted to 80 grams daily.

The treatments (Table I) were daily administered orally as a tablet, prepared as in Example 1. Groups 1, 2 and 3 were on a daily placebo treatment. Groups 4-5 were treated with 7α-methyl-17α-ethynyl-17β-hydroxy-estra-5(10)-en-3-one (OD-14; Tibolone; 6 or 2 mg daily); group 6 with 17β-estradiol (4 mg daily). Group 7 was on treatment with 17β-estradiol decanoate (150 µg in 1 ml arachis oil injected subcutaneously once a week).

Table I: Design of the experiment

Group	n	Treatment*	Dose	Diet	OVX
1	14	Placebo		cholesterol	Yes
2	13	Placebo		cholesterol	No
3	13	Placebo		normal	Yes
4	14	Org OD14	6 mg	cholesterol	Yes
5	13	Org OD14	2 mg	cholesterol	Yes
6 E2	14	Estradiol	4 mg	cholesterol	Yes
7 E2D	14	Estradiol decanoate	150 µg	cholesterol	Yes

*The doses were administered orally except for group 7 in which the dose was injected subcutaneously once a week.

During the experiment blood samples were drawn out of the central ear artery after sedation with Hypnorm (0.1 ml i.m.) (Janssen Pharmaceutics, Beerse, Belgium) before the daily treatment, at week 4,8,12,16 and 20, to monitor the plasma cholesterol levels and to measure, at week 17, plasma estradiol levels and plasma tibolone levels.

Twenty weeks after the start of the experiment animals were anaesthetized by an i.m. injection of Hypnorm (0.5 ml/kg). After blood sampling the rabbits were killed by exsanguination and the aortic arch, uterus and carotid artery removed for further analyses.

EVALUATION OF ATHEROSCLEROSIS

A: Fatty streaks

The aortic arch was dissected free, opened longitudinally and fixed in 2% paraformaldehyde. The tissue was then stained for lipids using 0.3% (w/v) Sudan Red. Colour photographs were taken of all segments. The percentage coverage of the aortic arch (Table II) with fatty streaks was assessed using image analysis (Context Vision Systems AB, Linköping, Sweden).

B: Vessel wall cholesterol measurement

After fatty streak measurement the aortic arch was minced in a dismembrator (Mikro-Dismembrator, B. Braun, Melsungen, Germany), followed by a lipid extraction according to the method of Bligh and Dyer (Can. J. Biochem. Biophys. 1959, 37, 911-917). The total cholesterol content in the chloroform/methanol extraction solution was, after evaporation under nitrogen and dissolution in methanol, determined using enzymatic CHOD-PAP method (cat. no. 1442341, Boehringer Mannheim, Germany) and evaluated in a spectrophotometer (wavelength 500 nm). The amount of protein in the tissue was determined by the method of Lowry.

C: Intimal thickening after de-endothelialisation

The left (airdried) carotid artery was dissected and fixed in 2% paraform-aldehyde containing 6.8% glucose. The right carotid artery was used as comparison. After fixation the tissue was divided in blocks with a length of 2

mm and embedded in paraffin (Paraplast plus®, Sherwood Medical Co, St. Louis, USA) using an automated tissue processor (Hypercenter XP, Shandon).

To measure intimal thickening (using image analysis) a specific staining method and a belonging image analysis application have been developed. Measurements were performed on 2 µm transverse sections which were treated with elastase (Serva Feinbiochemica Gmbh, Heidelberg, Germany) prior to elastin staining with Lawson solution (Boom, Meppel, the Netherlands) and light green (Sigma). Subsequently sections were airdried and mounted in Pertex (Leica Gmbh, Nussloch, Germany).

For morphological study both methylene blue/Azur II and hemotoxylin/eosin stained (2 µm) transverse sections were used. Smooth muscle cells and macrophages were detected with respectively α-actin antibodies (Sigma) and anti-macrophage antibodies (RAM11, DAKO, Glostrup, Denmark). For detection of bound antibodies goat anti-mouse ultra small gold conjugated secondary antibodies (Aurion, Wageningen, The Netherlands) and the immunogold-silver enhancement technique (SilvEnhance-LM Kit, Zymed) were used.

Images of the sections were obtained using a black and white video camera. (MX-5 , Adimec Image Systems BV, Eindhoven) mounted upon a light microscope (Axioplan, Zeiss, Jena, Germany). The video image was digitised and the intimal thickening was measured using a semi-automated image analysis application (Context Vision Systems AB, Linköping, Sweden).

Statistics: Data were expressed as mean ± S.E.M. unless otherwise specified. For testing statistical significance the Analysis of Variance (ANOVA) was used. The data were logarithmically transformed to normalize variations. A value of $P<0.05$ was considered to be significant.

RESULTS (Table II)

No significant difference in any of the variables measured were found between the ovariectomized animals (group 1) and the non-ovariectomized animals (group 2). This confirms that in the non-ovariectomized female rabbits the endogenous basal plasma estradiol levels are low.

Oral administration of 17β-estradiol (4 mg per day; group 6; E2) resulted in peak plasma estradiol levels of 238 pg/ml at 1h after administration, which was reduced to 18 pg/ml after 24 hours. Subcutaneous administered estradiol decanoate (150 µg per week; group 7; E2D) resulted in rather stable plasma estrogen levels over the day (about 60 to 70 pg/ml). The plasma levels indicate that both modes of administration of estradiol lead to effective plasma levels.

After 20 weeks of diet and of daily treatment, necropsy was performed to determine the accumulation of cholesterol and fatty streaks in the aortic arch and the advanced lesions in the carotid artery. Moreover the weight of the uterus was determined. The results are presented in the Table II.

The results show that both estradiol treatments (E2 or E2D) increased uterus weight (estrogenic effect). Org OD14 (2 and 6 mg per day) increased uterus weight to a similar extent as the estradiol treatments, confirming the equipot ncy of the doses used.

Despite this equipotent activity of the estrogen and Org OD14 treatments on the uterus the effect on cholesterol accumulation in the aorta and lesion formation in the aorta were different: 17β-estradiol (E2) treatment did not lead to a reduction in cholesterol accumulation, 17β-estradiol decanoate(ED2) treatment reduced cholesterol accumulation in the aortic arch with 46%, while Org OD 14 completely prevented cholesterol accumulation in the aortic arch at both concentrations studied.

17β-estradiol (E2) and 17β-estradiol decanoate (E2D) did not affect plasma cholesterol levels while Org OD14 strongly reduced the plasma cholesterol levels.

Fatty streak formation in the aortic arch was only slightly reduced by estrogen treatment while Org OD14 (nearly) completely prevented the fatty streak formation.

17β-estradiol (E2) had no effect on advanced lesion formation, following mechanical de-endothelisation, while 17β-estradiol decanoate (E2D) reduced advanced lesion formation. Histology showed that in placebo animals on a cholesterol diet the lesions consisted of smooth muscle cells and foam cells while in animals on a normal diet only smooth muscle cell were observed in the lesions. Histology of the E2D treated animals showed that the lesions still consisted of smooth muscle cells and foam cells. Org OD14 strongly inhibited the formation of advanced lesions. Lesion formation was even less than in the animals on a normal diet (control group). Histology showed that the lesions consisted only of smooth muscle cells.

The experiment demonstrates that while 17β-estradiol, 17β-estradiol decanoate and Org OD14, in clinically equivalent doses, are approximately equally potent on the uterus growth in rabbits, the effects of OD14 on plasma cholesterol, cholesterol accumulation in the aortic arch and advanced lesion formation in the carotid artery, are much more pronounced than those of 17β-estradiol.

Table II

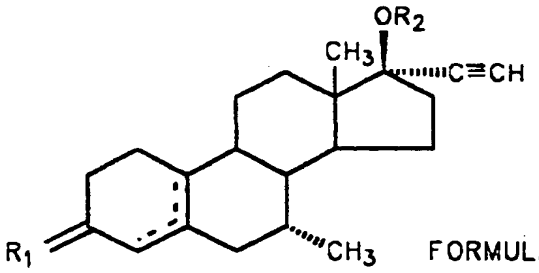
The effect of different treatments on the atherogenic diet induced morphologic changes in the aortic arch and carotid artery as well as the influence on body weight, plasma cholesterol and uterus weight as measured at the time point of necropsy (20 weeks after the start of the experiment).

	Controle Group 3	Placebo Group 1	Org OD14 Group 4	Org OD14 Group 5	Estradiol Group 6	Estradiol decanoate Group 7
Number of Rabbits	**13**	**9**	**13**	**12**	**13**	**11**
Body weight in grams	**2831 ± 50**	**2683 ± 95**	**2758 ± 41**	**2815 ± 50**	**2831 ± 58**	**2973 ± 52**
Uterus weight per 100 grams body weight	**0.08 ±0.01**	**0.09 ±0.01**	**0.24 ±0.06 ***	**0.29 ±0.03 ***	**0.31 ±0.02 ***	**0.37 ±0.04 ***
Mean plasma cholesterol exposure in mmol/L/day	**1.0 ± 0.1 ***	**26.9 ± 3.3**	**11.2 ± 1.5 ***	**9.0 ± 1.3 ***	**27.7 ± 2.8**	**30.0 ± 3.7**
Cholesterol level in aortic arch in nmol/mg protein	**45 ± 6 ***	**590 ± 126**	**52 ± 9 ***	**61 ± 11 ***	**521 ± 99**	**318 ± 58 ***
Fatty streak in aortic arch in % of arcus covered	**0.3 ± 0.2 ***	**34.5 ± 6.8**	**1.3 ± 0.8 ***	**1.4 ± 0.7 ***	**25.5 ± 5.2**	**28.1 ± 4.1**
Advanced lesions in carotid artery: intimal surface in mm^2	**0.22 ± 0.03 ***	**0.44 ± 0.10**	**0.13 ± 0.03 ***	**0.14 ± 0.02 ***	**0.30 ± 0.06**	**0.23 ± 0.06 ***

* $p < 0.05$ compared with placebo (group 1)

Claims:

1. Use of a 7α-methyl-17α-ethynyl-estrane derivative having the general formula I



FORMULA I

wherein

R_1 = H(OR_3) or O;

R_2 = H or (C_{1-18})Acyl;

R_3 = H or (C_{1-18})Acyl;

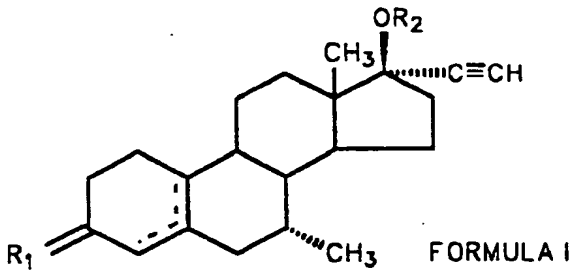
and the dotted line represents a double bond in the 4,5- or the 5,10-position, for the manufacture of a medicament for the prophylaxis or the treatment of atherosclerosis.

2. Use according to claim 1, wherein R_1 = O.

3. Use according to claim 1 or 2, wherein the dotted line represents a double bond in the 5,10-position.

4. Use according to claim 1, wherein the a 7α-methyl-17α-ethynyl-estrane derivative is 7α-methyl-17α-ethynyl-17β-hydroxy-estra-5(10)-en-3-one.

5. A method of inhibiting the process of atherosclerosis comprising administering to a mammal an atheroprotective amount of a 7α-methyl-17α-ethynyl-estrane derivative having the general formula I



FORMULA I

wherein

R_1 = H(OR_3) or O;

R_2 = H or (C_{1-18})Acyl;

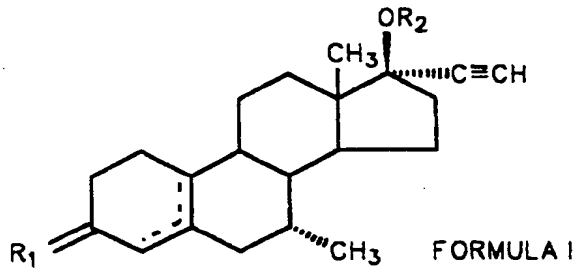
R_3 = H or (C_{1-18})Acyl;

and the dotted line represents a double bond in the 4,5- or the 5,10-position.

6. The method according to claim 5 wherein the mammal is human.

Abstract.

The invention relates to the use of a 7α-methyl-17α-ethynyl-estrane derivative having the general formula I



FORMULA I

wherein R_1 = H(OR_3) or O; R_2 = H or (C_{1-18})Acyl; R_3 = H or (C_{1-18})Acyl; and the dotted line represents a double bond in the 4,5- or the 5,10-position for the manufacture of a medicament for the prophylaxis or the treatment of atherosclerosis.